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Myelodysplastic Syndromes With Nephrotic Syndrome

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It is sometimes reported that the immunological abnormalities in myelodysplastic syndromes (MDS) induce autoimmune disease (i.e., acute systemic vasculitic syndrome, chronic cutaneous vasculitis, polyneuropathy, relapsing polychondritis, and steroid-responsive pulmonary disorders). We investigated the clinical features of patients with MDS accompanied by nephrotic syndrome. We enrolled 125 patients with MDS who were admitted between January 1979 and May 1996 in this study. The renal function was assessed based on the laboratory data and the findings at the physical examination. The diagnoses of nephrotic syndrome and glomerular disease were established when 24-hr urinary excretion was more than 3.5 g and serum total protein was less than 6.0 g/dl, and when the 24-hr protein excretion was more than 1.5 g. Five patients (4%) had glomerular disease, and three (2.4%) had nephrotic syndrome. Of the five patients with glomerular disease, two had refractory anemia (RA), and three had chronic myelomonocytic leukemia (CMMOL). Three of the total 11 patients with CMMOL were diagnosed as having nephrotic syndrome. Among the CMMOL patients, those with nephrotic syndrome showed higher absolute monocyte numbers than did those without nephrotic syndrome (8830 ± 4677/μl vs. 3061 ± 2887/μl, $P = 0.03$). One CMMOL patient was treated with VP-16 and hydroxyurea. As the white blood cell count in this patient decreased, the 24-hr urine protein excretion and the serum tumor necrosis factor alpha level decreased. The relationship between nephrotic syndrome and CMMOL was not clear. High monocyte count and the serum cytokines in MDS patients may play a partial role in the evolution of glomerulonephritis, and CMMOL may be closely related to nephrotic syndrome. Am. J. Hematol. 60:200–204, 1999.

Key words: myelodysplastic syndromes; chronic myelomonocytic leukemia; nephrotic syndrome; tumor necrosis factor alpha

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders, as defined by the French-American-British (FAB) Cooperative Group [1]. They share impairment of differentiation capacity, which is the fundamental abnormality. MDS are sometimes accompanied by autoimmune diseases (i.e., acute systemic vasculitic syndrome, chronic cutaneous vasculitis, polyneuropathy, relapsing polychondritis, and steroid-responsive pulmonary disorders [2–6]).

It was reported recently that the etiology and progression of nephrotic syndrome are related to immunological abnormality [7,8]. And it has been reported that hematological malignancies, including malignant lymphoma [9–12], and chronic lymphocytic leukemia (CLL) [13–15], are sometimes accompanied by proteinuria, which often diminishes after chemotherapy. According to these reports, hematological malignancies may be related to the induction of nephrotic syndrome. We investigated the clinical features of patients with MDS with nephrotic syndrome, and we discuss herein the relationship between MDS and nephrotic syndrome.

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TABLE I. Clinical and Laboratory Data in Patients With MDS Accompanied by Renal Disease*

	Patient				
	No. 1	No. 2	No. 3	No. 4	No. 5
Sex	F	F	F	M	F
Age	51	73	71	79	71
Type of MDS	RA	RA	CMMOL	CMMOL	CMMOL
Survival (months)	28	36	12	3	2
Hematological findings					
Hb (g/dl)	7.0	5.3	7.2	10.3	11.1
WBC (10^9/l)	0.5	6.3	44.7	36.6	20.6
Plt (10^9/l)	96	326	51	60	30
Peripheral blood					
Myeloblast (%)	0	0	4.0	1.5	3.0
Monocyte (%)	2.0	2.0	24.0	33.5	17.0
Bone marrow					
Myeloblast (%)	0	0	4.2	1.5	3.0
Monocyte (%)	2.0	2.0	7.6	36.6	14.2
Karyotype	Normal	Normal	46,XX,20p-q-	Normal	45,XX,-7,17p+
LDH (IU/l)	245	340	2848	592	1139
S-Lysozyme (μg/ml)	5.2	4.2	55.0	298.5	104.0
U-Lysozyme (μg/ml)	Not done	Not done	320	1520	870
Renal findings					
Urine protein excretion (g/day)	2.0	1.8	4.8	3.7	3.5
U-protein/U-creatinine	2.0	2.4	5.2	Not done	3.9
Hematuria	2+	2+	3+	—	±
Total protein (mg/dl)	3.6	4.2	5.3	6.0	6.0
Serum albumin (mg/dl)	3.2	1.0	2.8	3.3	2.0
BUN (mg/dl)	36	12	18	21	25
Creatinine (mg/dl)	3.2	1.0	1.2	1.3	1.6
CCr (ml/min)	15.2	65.2	36.7	Not done	30.2

*MDS, myelodysplastic syndromes; RA, refractory anemia; CMMOL, chronic myelomonocytic leukemia; Hb, hemoglobin; WBC, white blood cell; Plt, platelet; LDH, lactate dehydrogenase; BUN, blood urea nitrogen.

PATIENTS AND METHODS

We studied the hematological and clinical status of 125 patients with de novo MDS who were newly diagnosed between January 1979 and May 1996. According to the FAB criteria [1], 70 of these patients were classified as having refractory anemia (RA), 5 as having RA with ringed sideroblasts, 25 as having RA with excess of blasts (RAEB), 14 as having RAEB in transformation (RAEB-T), and 11 as having chronic myelomonocytic leukemia (CMMOL). In each patient, the differential counts of circulating leukocytes for 200 leukocytes and the percentage of bone marrow blasts in 500 nucleated cells were evaluated.

The renal function was assessed based on the laboratory data and results of the physical examination. We measured 24-hr urinary protein excretion of all 125 patients. These data included the levels of serum creatinine, and blood urea nitrogen (BUN), the 24-hr protein excretion, and the presence or absence of hypertension. The diagnosis of nephrotic syndrome and glomerular disease were established when 24-hr urinary excretion was more than 3.5 g and serum total protein was less than 6.0 g/dl, and when the 24-hr protein excretion was more than 1.5 g. No patient met the criteria for systemic lupus erythematosis or showed any evidence of diabetes mellitus or other systemic diseases known to cause glomerulonephritis. The renal biopsy specimens were examined by light microscopy, and immunofluorescence (IF) in one case. Statistical analysis was performed according to Student's *t* test and values are expressed as mean ± standard deviation.

RESULTS

The clinical and laboratory data for each of the five patients with glomerular disease (more than 1.5 g urine protein of 24 hr) are summarized in Table I. Two of these patients met the FAB criteria [1] for RA, and three met the criteria for CMMOL. The mean age of these five patients was 69 years (range, 51–79 years), and there was a preponderance of women (four women and one man). Because three of the patients had CMMOL, the white blood cell counts at the initial diagnosis were higher than those in the other patients with MDS. Abnormal karyotype was detected in the two patients with CMMOL.

The 24-hr urine protein excretion ranged from 1.8 g to

TABLE II. Nephrotic Syndrome Group and Non-NS Group in CMMOL*

	NS group	Non-NS group	*P*
Number	3	8	
Sex (M/F)	0/3	2/6	
Hb (g/dl)	9.53 ± 2.06	9.57 ± 2.23	0.98
WBC (10^9/l)	33.97 ± 12.26	14.55 ± 13.56	0.06
Peripheral blood			
Myeloblast (%)	2.83 ± 1.25	2.56 ± 6.84	0.95
Monocyte (%)	24.8 ± 8.2	22.5 ± 5.9	0.61
Mono (Abs.)	8830 ± 4678	3061 ± 2887	0.03
Plt (10^9/l)	137 ± 141	115 ± 77	0.75
Bone marrow			
Myeloblast (%)	6.3 ± 2.97	6.1 ± 7.35	0.97
Monocyte (%)	10.9 ± 4.67	16.2 ± 9.61	0.48
LDH (IU/l)	1312 ± 1353	503 ± 347	0.12

*NS, nephrotic syndrome; Hb, hemoglobin; WBC, white blood cell; Plt, platelet; LDH, lactate dehydrogenase.

4.8 g. The qualitative analysis of urine protein and urine blood ranged from 2 to 3+ and from − to 3+, respectively. Proteinuria was associated with hematuria in four of the five patients. The serum creatinine level was elevated greater than 1 mg/dl in all five patients, and it exceeded 3 mg/dl in one patient. The estimated creatinine clearance ranged from 15.2 to 65.2 ml/min. Hypertension was not recognized in any patient. Renal biopsy performed in one patient with RA disclosed mesangial proliferative glomerulonephritis.

Three patients were diagnosed as having nephrotic syndrome. According to the FAB criteria, they were classified as having CMMOL. Among the total of 11 CMMOL patients, those with and without nephrotic syndrome showed no significant difference for hemoglobin, white blood cell count, platelet count, or lactate dehydrogenase level, but those with nephrotic syndrome showed higher absolute monocyte number compared with those without nephrotic syndrome (8830 ± 4677/μl vs. 3061 ± 2887/μl, respectively, $P = 0.03$) (Table II). One CMMOL patient (patient no. 3) was treated with VP-16 and hydroxyurea. The urine protein excretion gradually decreased from 4.8 g/day on admission to 0.2 g/day after this chemotherapy. The serum level of tumor necrosis factor alpha (TNF alpha) also decreased from 52.3 pg/ml to 12.2 pg/ml after chemotherapy.

DISCUSSION

In general, nephrotic syndrome occurs in 0.015% of the normal population [17]. In this study, we found that, of 125 patients with MDS, five (4%) had glomerular disease and three (2.4%) had nephrotic syndrome. Thus, the incidence of nephrotic syndrome seems to be elevated in MDS, particularly CMMOL, compared with that in the normal population.

Immunological abnormalities are seen frequently in the clinical course of MDS. Functional abnormalities of B cells and T cells, and increased or decreased levels of immunoglobulins, have also been reported [14,16]. Autoimmune diseases (such as acute systemic vasculitic syndrome, chronic cutaneous vasculitis, polyneuropathy, relapsing polychondritis, and steroid-responsive pulmonary disorders) are common in patients with MDS [2–6].

Nephrotic syndrome occurs frequently in association with various malignant processes, including some carcinomas, and hematological malignancies (malignant lymphoma [9–11], and CLL [13–15]). An association between various solid tumors and membranous glomerulonephritis was reported. The reported incidence of glomerulonephritis associated with solid tumor ranged from 3% to 13%, and it is as high as 22% in patients over 60 years of age [18]. The incidence of glomerulonephritis is 49% in patients with lung cancer, 12% in those with colon cancer, and 8% in those with gastric cancer. The close relationship between glomerulonephritis and solid tumor was confirmed in an investigation revealing positive staining for cancer antigens in kidney biopsy specimens [19].

In hematological malignancies, many authors have reported that malignant lymphoma and CLL have a relationship with glomerulonephritis. In Hodgkin's disease, the most common lesion is minimal change glomerulonephritis, although membranous or proliferative lesions have also been reported [9]. Eagan and Lewis [20] reviewed 52 cases of Hodgkin's disease with nephrotic syndrome, and found minimal change nephrotic glomerulonephritis in 50% of them. Abnormalities of lymphocyte function in Hodgkin's disease have often been reported. It has been suggested that impairment of T-cell mediated immunity induces minimal change nephrotic glomerulonephritis in Hodgkin's disease [9,21]. In non-Hodgkin's lymphoma, minimal change glomerulonephritis and mesangial proliferative glomerulonephritis are less frequently observed than in Hodgkin's disease [10,22]. It is reported that CLL is often accompanied by glomerular injury. These patients often have membranoproliferative glomerulonephritis (MPGN). This type of MPGN is reported to be clearly related to the cryoglobulinemia or M-proteinemia accompanying with CLL [12]. Several autoimmune complications were observed in CLL patients, and induction of complete remission of nephrotic syndrome was observed after chlorambucil therapy without steroids [13–15].

The relationship between nephrotic syndrome and CMMOL was not clear.

Nephrotic syndrome may occur due to infiltration of a high number of monocytes of CMMOL. It is reported that the infiltration of monocytes in renal glomeruli was observed in different types of glomerulopathy, and the monocyte count was related to the activity of glomerulopathy [23,24]. Among our patients with CMMOL,

those with nephrotic syndrome showed a higher absolute monocyte number than did those without nephrotic syndrome. Then, the infiltration of monocytes in the kidneys may play a role in induction of nephrotic syndrome.

It is reported that increased serum and urine lysozyme may lead to tubular dysfunction and the induction of interstitial nephritis [25,26]. All 3 of our CMMOL patients with nephrotic syndrome have high serum and urine lysozyme. Therefore, lysozyme in CMMOL patients may be related to be induction of nephrotic syndrome. All of the previously reported cases of MDS associated with glomerulonephritis were also cases of CMMOL [27].

Concerning the pathogenesis of glomerulonephritis, particularly minimal change nephrotic syndrome, it has been thought in recent years that a cytokine released by circulating blood mononuclear cells could alter the permeability of the glomerular capillary wall [7]. The participation of TNF alpha, a cytokine mainly produced by monocytes, was suspected to be a main cause of nephrotic syndrome. Moreover, it was reported that patients with nephrotic syndrome in the active state had higher serum TNF alpha levels and TNF alpha production by monocytes than do patients in remission and controls [28,29].

In MDS, there are a few reports that the serum TNF alpha levels in CMMOL patients are significantly higher than those in patients with other FAB subgroups [30]. The monocytes of CMMOL patients have a tendency to infiltrate into visceral organs including the kidney, and to secrete TNF alpha at high levels as in any condition resembling infection. All three of the patients with nephrotic syndrome included in this study had CMMOL. The serum level of TNF alpha in one of these patients was higher than normal. After chemotherapy for CMMOL, the nephrotic syndrome in this patient improved, and the serum level of TNF alpha was normalized. In CMMOL patients, monocytes may be related to the production of TNF alpha. According to these data, TNF alpha in CMMOL patients may play a partial role in induction of nephrotic syndrome.

We conclude that CMMOL may be closely related to nephrotic syndrome.

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